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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

12

Office Action Summary	Application No.	Applicant(s)	
	09/966,545	FERNANDES ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-22,27-29,31,32,35 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-22,27-29,31,32,35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Status of Application, Amendments and/or Claims

The amendment filed 04 September 2003 has been entered in full. Claims 23-26, 30, 33 and 34 were cancelled. New claims 35 and 36 were added. Claims 18-22, 27-29, 31, 32, 35 and 36 are under examination.

The Gerlach Declaration under 37 CFR 1.132, filed 04 September 2003, was entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The rejection of claims 20, 21, 24 and 25 under 35 USC 112, second paragraph as set forth at pages 9-10 of the previous Office Action (04 March 2003) is *withdrawn* in view of the amendment (04 September 2003).

Claim Rejections - 35 USC § 101

Claims 18-22, 27-29, 31, 32, 35 and 36 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. The basis for this rejection is set forth at pages 2-5 of the previous Office Action (04 March 2003).

Applicants argue that the nucleic acids of the claimed invention have a specific, substantial and credible utility and are therefore, patentable under 35 USC 101. Applicants assert that the SECX clone 4324229-2 can be used in the detection and/or

differentiation of various forms of cancer and in a variety of cancer related diagnostic applications. In support of these assertions, Applicants submit a Declaration under 37 CFR 1.132 by Valerie Gerlach, Ph.D, an employee of CuraGen Corp, the assignee of the instant application. Applicants state that the data presented in the Appendix of the Declaration depicts the scaled results of real time quantitative polymerase chain reaction-based gene expression analysis performed using a SECX clone 4324229-2 gene specific primer probe set to measure the relative SECX clone 4324229-2 expression levels in normal cells or tissues and pathological tissue samples. The Relative Expression Score for each sample indicates the relative quantity of a SECX clone 4324229-2 transcript, with 0.0 indicating no detectable expression and 100.0 indicating highest detectable expression level.

Dr. Gerlach states that the quantitative expression of 4324229-2 (SEQ ID NO:15) was assessed using microtiter plates containing RNA samples from a variety of normal and pathology-derived cells, cell lines and tissues. Normalized RNA was spotted in individual wells, PCR cocktails included a single gene specific probe and primer set or two multiplexed probe and primers sets. Reverse transcription was performed, results were recorded as CT values and plotted using a log scale, with the difference in RNA concentrations between a given sample and the sample with the lowest CT value being represented as 2 to the power of delta CT. Dr. Gerlach states that expression of gene SEQ ID NO:15 was higher in normal kidney tissue compared to kidney tumors but higher in lung cancer when compared with normal lung tissue. Dr. Gerlach also states that SEQ ID NO:15 was higher in breast cancer when compared to normal breast tissue

including two pairs of samples with tumor and match normal adjacent tissue. Expression was upregulated in two out of two bladder cancer samples and in one out of two ovarian cancer samples. Dr. Gerlach concludes by stating that the expression of instant gene or protein is useful to detect and differentiate kidney, lung, breast and ovarian cancer tissues from normal tissues.

The Gerlach Declaration filed on 04 September 2003 under 37 CFR 1.131 has been considered but is ineffective to overcome the 35 USC 101/112 rejection. The instant claims are drawn to the nucleic acid (SEQ ID NO:15) and the nucleic acid encoding the polypeptide (SEQ ID NO:16). Therefore the polynucleotide must have utility and the use of the polynucleotide in the production of the polypeptide must have utility. The Examiner will first address the lack of utility for the polynucleotide.

The data presented in the Gerlach Declaration has many drawbacks. The use of tumor cell lines in tumor marker data is a problem because tumor cell lines are not equal to primary tumor tissue. The cell culturing process alters gene expression and selects subgroups of cells such that the cultured cells are no longer representative of the diseased tissue. Furthermore, in tumor cell lines analyzed by PCR, insignificant expression levels are amplified until they appear significant. From the Declaration it is not apparent that there is control tissue (normal and primary tumor) for every tumor cell line. Amplification of proto-oncogenes and aneuploidy is commonly observed in human tumors. The Gerlach Declaration fails to disclose that SEQ ID NO:15 was used in cytogenetic analytic techniques such as in situ hybridization or comparative genomic hybridization to discern aneuploidy in primary tumors. Furthermore, a slight amplification

of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Thus amplification would have to be confirmed to be significant using aneuploidy and normal controls, meaning gene copy number is truly increased. The Gerlach declaration fails to disclose this.

The Gerlach Declaration discloses a wide range of tissues that express the gene. In fact, the gene is inconsistently expressed in cancer tissues. It is found at high levels in one strain of kidney cancer (10C6), and is low in two other kidney cancer cell lines (10A8 and 10AA). It is expressed in moderate levels in one line of lung cancer cells (A549), and is very low in two others (NCI-H23 and HOP-62). In fact, the gene is expressed in a wide variety of cancerous tissues, but reaches highest expression levels in normal tissues such as hippocampus and cerebral cortex. With the wide range of tissue types showing high expression of the instant invention, and the lack of correlation with a specific disease, it would be difficult to envision use of the polynucleotide as a diagnostic marker for any proliferative disease. Furthermore, the original disclosure did not *specifically assert* that the instant gene (4324229-2) had increased and decreased levels of expression in those *specific tissues* as cited in the Gerlach Declaration, thus the specification did not assert this utility at the time of filing.

The nucleic acid encoding the polypeptide (SEQ ID NO:16) lacks a utility because there is no information regarding the level of protein expression, activity or role in cancer. One skilled in the art would not readily use the nucleotides encoding the claimed polypeptide for tissue-typing in a real world sense as the protein is not specific to one tissue or type of tissue and is not associated with any disease or disorder. In

addition, protein expression shows a poor correlation with mRNA expression. The Examiner has cited Haynes *et al.* to demonstrate this. Haynes *et al.* (Electrophoresis 19:1862-1871, 1998) studied 80 proteins relatively homogenous in half-life and expression level and found no strong correlation between protein and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. Haynes concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (page 1863, 2nd paragraph, and Figure 1).

The Gerlach Declaration fails to disclose a clear nexus between any specific gene disease state and an alteration in level or form of the gene/protein. Further experimentation is required before the this asserted utility is specific and substantial. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

Claims 18-22, 27-29, 31, 32, 35 and 36 also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The basis for this rejection is set forth at pages 5-7 of the previous Office Action (04 March 2003).

Applicant incorporates their response to the rejection under 35 USC 101 in response to the rejection under 35 USC 112, first paragraph. Applicants arguments have been fully considered but are not found to persuasive for the reasons discussed above in the maintained rejection in 35 USC 101.

Applicants further state that the pending claims are not directed to any mutant, variant and/or fragment of a nucleic acid sequence encoding a polypeptide of SEQ ID NO:16. Rather, these claims are directed to a nucleic acid encoding a polypeptide of SEQ ID NO:16, or a specific subset of nucleic acids that are at least 90% identical to the nucleic acid encoding a polypeptide of SEQ ID NO:16. Applicants contend that one of ordinary skill in the art could identify and prepare nucleic acids that are 90% identical to the nucleic acid encoding a polypeptide of SEQ ID NO:16 with routine experimentation using standard techniques known to those skilled in the art. Applicants contend that the instant specification discloses the use of computer programs known in the art to determine the homology between nucleic acid sequences.

Applicants' arguments have been fully considered but not deemed persuasive. The asserted utility is that SECX clone 4323229-2 (SEQ ID NO:15) can be used in the detection and/or differentiation of various forms of cancer and in a variety of cancer-related diagnostic applications. It is unpredictable if the degenerate polynucleotides, i.e. a nucleic acid sequence at least 90% to the nucleic acid sequence encoding a polypeptide of SEQ ID NO:16, would be amplified in any cancer. There is a difference between the ability to identify a nucleic acid sequence at least 90% to the nucleic acid sequence encoding a polypeptide of SEQ ID NO:16 versus the ability to *make* those

with at least 90% to the nucleic acid sequence encoding a polypeptide of SEQ ID NO:16 *that retain function* in order to meet the make and use the standard.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

Claims 18-22, 27, 28, 31 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth at pages 7-9 of the previous Office Action (04 March 2003).

Applicants state that the pending claims have been amended to remove all references to complements, mutants and/or variants of the nucleic acid sequences presented in Figures 1-13 and 18-19 of the instant specification. Claim 18 has been amended to recited isolated nucleic acids comprising a nucleic acid sequence encoding a polypeptide of SEQ ID NO:16 or a nucleic acid sequence that is at least 90% identical to the nucleic acid encoding a polypeptide of SEQ ID NO:16. Applicants cite pages in the specification for support. Applicants maintain that the pending claims are fully described in the specification.

Applicants' arguments have been fully considered but not deemed persuasive. The instant claims recite "a nucleic acid sequence at least 90% identical to the nucleic

acid sequence encoding a polypeptide of SEQ ID NO:16". The specification discloses only a structural feature of the nucleotide sequence of SEQ ID NO:15. The claims, however, encompass genes yet to be discovered. There is no disclosure regarding the coding capacity of any of the sequences recited. Defining the sequences in functional terms would not suffice in the absence of a disclosure of structural features or elements of a cDNA that would encode a protein having a stated function. The pages Applicants recite do not *explicitly* teach what sequence changes should be made. There is no description of variants of a nucleic acid sequence encoding a polypeptide of SEQ ID NO:16 that exist, while still maintaining a function. Specific, not general guidance is what is needed. The disclosure fails to describe the common attributes or characteristics that identify the members of the genus, and because the genus is variant, SEQ ID NO:15 alone is insufficient to describe the genes. The disclosure fails to provide a representative number of species to describe the genus. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 112, Second Paragraph

Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 29 is drawn to the cell of claim 82. Claim 29 is indefinite because it does not refer back to the preceding claim.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on 9:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD
November 17, 2003

YVONNE EYLER, PH.D
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